DOI:
10.1097/MCC.0000000000000460

Document Version
Peer reviewed version

Septic shock resuscitation in the first hour

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Author contributions

All authors developed the outline. NS wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content

Sources of support

Dr Shankar-Hari is supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. Dr. Lamontagne is supported by the Fonds de Recherche du Québec – Santé (33132).

Structured abstract

Purpose of review

We review the recent advances in the initial approach to resuscitation of sepsis and septic shock patients.

Recent findings

Sepsis and septic shock are life threatening emergencies. Two key interventions in the first hour include timely antibiotic therapy and resuscitation. Before any laboratory results, the need for resuscitation is considered if a patient with suspected infection has low blood pressure or impaired peripheral circulation found at clinical examination. Until now, this early resuscitation in sepsis and septic shock was supported by improvements in outcome seen with goal-directed therapy. However, three recent, goal-directed therapy trials failed to replicate the originally reported mortality reductions, prompting a debate on how this early resuscitation should be performed. As resuscitation if often focussed on macrociculatory goals such as optimising central venous pressure, an argument to explore for lack of outcome benefit in the newer trials is the discordance between microcirculatory and macrocirculatory optimisation during resuscitation. Vasoactive drugs and large volume resuscitation associated positive fluid balance, are independently associated with worse clinical outcomes in critically ill sepsis and septic shock patients. As lower blood pressure targets and restricted volume resuscitation are feasible and safe, should we use a revised blood pressure target to reduce the adverse effects of catecholamine' and excess resuscitation fluids. Evidence guiding fluids, vasopressor and inotrope selection remains limited.

Summary

Though the early resuscitation of septic shock is key to improving outcomes, ideal resuscitation targets are elusive. Distinction should be drawn between microcirculatory and macro-circulatory changes, and corresponding targets. Common components of resuscitation bundles such as large volume resuscitation and high-dose vasopressors may not be universally beneficial. Microcirculatory targets, individualised resuscitation goals and reassessment of completed trials using the updated septic shock criteria should be focus areas for future research.

Key words: Sepsis, septic shock, resuscitation, microcirculation

Septic shock resuscitation in the first hour

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection(1). In this context, the organ dysfunction is identified clinically by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more(1, 2). Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone(1). The clinical criteria for identifying septic shock patients is a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia(3). Resuscitation is the key intervention for treating macro and microcirculatory abnormalities commonly observed in sepsis and septic shock patients(4) and resuscitation also forms part of the 3-hour and 6-hour bundles proposed in the Surviving Sepsis Campaign Guidelines(5). In this review, we discuss sepsis related microcirculation and macro-circulation abnormalities, resuscitation goals in guidelines, microcirculation as a focus of early resuscitation, and emerging evidence on fluids, vasoactive active drugs and adjuvants targeted during resuscitation in sepsis and septic shock.

Microcirculation and macro-circulation abnormalities are common in sepsis and septic shock

Microcirculation refers to circulation within the blood vessels less than 100 to 150 micrometer in diameter (such as arterioles, capillaries, venules, and lymphatics) and the associated cells such as endothelium, smooth muscle, erythrocytes, leukocytes and platelets. The tools required to measure microcirculatory flow directly are not routinely available. Notwithstanding, tissue perfusion based markers(6) such as lactate, mixed / central venous oxygen saturation ($ScvO_2$), and central venous-arterial partial pressure of carbon dioxide difference ($DeltaPCO_2$)(7, 8), constitute indirect markers of adequate global microcirculation. Microcirculation could also be assessed to understand the homogeneity in blood flow by assessing number of patent capillaries, referred to as functional capillary density' [FCD].

In sepsis, the microcirculation is profoundly altered due to local and systemic host responses. The endothelial barrier is altered from it natural continuous and anticoagulant barrier between circulating

blood and tissue into a disrupted barrier that is enhances coagulation, extravasation of fluids and activated leukocytes creating a vicious cycle. This perpetuates inflammation, coagulopathy and endothelial injury(9). The associated impaired vascular smooth muscle tone, relative hypovolemia and a reduction in the FCD results in a heterogeneous combination of microcirculatory units lose their ability to regulate vascular tone and inappropriately constricted arterioles coexist with vasodilated units. These changes result in inefficient microcirculation resulting in an oxygen partial pressure (PO_2) gap evidenced by the reduced capillary PO_2, increased venous PO_2 and impaired mitochondrial oxygen extraction(10, 11).

The circulation in larger blood vessels is referred to as macro-circulation. Indicators of macro-circulation include central venous pressure (CVP), pulmonary wedge pressure (PAWP), arterial blood pressure (ABP), cardiac output (CO), arterial oxygen content (CaO_2) and delivery (DO_2). Similar to microcirculatory changes, the macrocirculation abnormalities in sepsis are also heterogeneous. In addition, there is an acute reversible myocardial depression affecting both ventricles, with altered myocytes and gene expression abnormalities suggestive of impaired sarcomere contraction and impaired excitation-contraction coupling(12, 13).

Early resuscitation in sepsis and septic shock

In 2001, Rivers et al, reported a 263 patient single centre randomised controlled trial (RCT) of early goal-directed therapy (EGDT) versus standard care for patients with severe sepsis or septic shock, that showed 16% absolute reduction in in-hospital mortality with EGDT. This EGDT consisted of firstly achieving the macro-circulation goals (CVP>=8-12mmHg, MAP>=65mmHg), followed by the microcirculation target of ScvO2>=70%. The interventions to achieve these macro-circulation goals were fluids and vasopressors and those for microcirculation goals were red blood transfusion to a haemoglobin >10g/L and/or inotropic agents to improve cardiac output. The key differences between the EGDT arm and usual care arm in term of interventions administered between 0 hours and 6 hours were – significantly greater volume of fluids, red blood cells, and inotropic agents. This trial formed the basis for the resuscitation goals in the previous Surviving Sepsis Campaign Guidelines(14). Goals during the first 6 hours of resuscitation: CVP = 8–12; MAP ≥ 65 mm Hg; urine output ≥ 0.5 mL/kg/hr and $ScvO_2$ (superior vena cava) or mixed venous oxygen saturation >=70% or 65%, respectively.

Between 2008 and 2014, three further multicentre RCTs compared EGDT to usual care, using a similar protocol to Rivers et al, enrolling a total of 4211 patients, from the United States (Protocolized Care for Early Septic Shock [ProCESS]), Australasia (Australasian Resuscitation in Sepsis Evaluation [ARISE]), and the United Kingdom (Protocolised Management in Sepsis [ProMISe]). In addition to trial level meta-analyses (15), the authors also harmonised data from these three trials and reported an individual patient level meta-analysis (IPDMA) (16), to explore the overall average treatment effect and key pre-defined subgroups effects of EGDT compared to usual care. The 90-day mortality did not differ between the EGDT therapy (24.9%) and usual care (25.4%) groups with a non-significant adjusted odds ratio (95% confidence interval) of 0.97 (0.82 – 1.14). The EGDT treatment effect did not vary by severity of illness. Based on these results, the current Surviving Sepsis Campaign Guidelines(5) strongly recommend administering at least 30 mL/kg of intravenous crystalloid fluids within the first 3 hours, whilst acknowledging that this is based on low quality of evidence). These guidelines also recommend a target MAP>=65mmHg and suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels, which is a weak recommendation based on low quality evidence, but addresses a microcirculation goal.

Is there a role for targeting microcirculation during early resuscitation?

The microcirculation goals addressed in RCTs include a reduction in serum lactate concentrations compared to either $ScvO_2$ in the emergency department (The LactATES trial (17)) or to usual care in the ICU (18). The LactATES trial was a non-inferiority RCT in 300 patients and compared the control group who received targeted resuscitation to meet thresholds of CVP, followed by MAP, and then ScvO2 of 70% or more to the lactate clearance group that had similar targeted thresholds in CVP, MAP, and then lactate clearance of 10% or more. This trial highlighted that lactate clearance is non-inferior to $ScvO_2$ based resuscitation. Of note, a pre-specified subgroup analysis from this trial highlighted that achievement of only the $ScvO_2$ goal was associated with a higher mortality compared to achievement of only the lactate clearance goal only (41% vs 8% and difference in proportion = 33%; 95% CI = 9% to 55%). Whilst these underpowered subgroup analyses needs testing in RCTs prior to clinical adoption(19), it does highlight the value of studying lactate kinetics. In the ICU, Jansen et al evaluated a complex protocol to target a lactate clearance of 20% or more. Although, there was no difference in unadjusted mortality between the usual care arm and lactate clearance arm, the covariate adjusted OR was significantly lower in the lactate clearance arm. Patients in the lactate

clearance arm received more fluids and, as stipulated by the experimental protocol, 42.5% received vasodilators during the first eight hours of resuscitation with the objective of 'opening' microcirculatory units. This approach challenges the more traditional goals of resuscitation (e.g. MAP of 65 mmHg). Vasopressors, which are commonly used to achieve MAP targets, could be reduced to the extent that minimal perfusion can be maintained at lower MAP values and, ultimately, administering vasodilators therapy could improve microcirculatory flow. However, while lactate clearance is undisputedly a favourable prognostic sign(20), high lactate levels are not specific for tissue dysoxia in sepsis and catecholamines' directly increase lactate levels via increased glycolysis(21). Furthermore, the Surviving Sepsis Campaign guideline panel made a weak recommendation for lactate-guided resuscitation protocols, based on low quality evidence, and did not address vasodilators, citing methodological limitations in the supporting literature.

Arteriovenous CO2 gradients constitute another potential resuscitation target(22). In theory, the difference between venous and arterial carbon dioxide blood content increases in proportion with the mismatch between cardiac output and the production of carbon dioxide. Elevated DeltaPCO_2 gradients (the normal range is 2-6 mmHg) may indicate inadequate blood flow relative to metabolism before lactate levels rise. However, CO_2 metabolism is complex and the value of DeltaPCO_2 gradients as resuscitation targets hinges on numerous assumptions. Moreover, the overall effects of resuscitation protocols guided by DeltaPCO_2 gradients remain unknown. Finally, in a provocative study, Marik and colleagues highlight the potential clinical benefits of combined early administration of intravenous vitamin C, together with corticosteroids and thiamine with biological plausibility arguments that point towards the microvasculature effects of this intervention(23). In summary, well designed and adequately powered experiments on the role of microvascular resuscitation in sepsis and septic shock patients are urgently needed.

Fluids

The theoretical goal of administration of fluid in the initial resuscitation of septic shock is the restoration of stressed intravascular volume and optimization of ventricular preload. The amount and type of fluid therapy remain contentious. Whilst fluid boluses may augment immediate haemodynamic parameters, concerns exist in regard to the transient nature of effect, the impact on the microcirculation and risk of iatrogenic complications (24-26). There remains a similar lack of clarity around the most appropriate type of fluid to administer in the early phases of resuscitation in septic

shock. Hydroxyethyl starch solutions are no longer widely recommended based on a lack of overall benefit and potential harm (27). Similarly, the potential efficacy signal in the sepsis subgroup for Albumin based resuscitation could not be confirmed in a recent RCT(28). In the absence of any clearly demonstrated benefit for colloids, initial crystalloid resuscitation is still recommended in the 2016 Surviving Sepsis guidelines, although concerns persist about the multiple potential side effects of resuscitation with normal saline including renal, pro-inflammatory, anticoagulant and acid-base associations. Balanced solutions have theoretical advantages, although a clear benefit is yet to be consistently demonstrated(12). Whichever fluid and volume is chosen, with limited and conflicting evidence in the setting of septic shock, it is important that the therapeutic agent is considered a drug, and administered with such caution.

Large volumes of resuscitation fluids administered to septic shock patients result in a positive cumulative fluid balance. This increasing cumulative balance impairs microcirculation and is an independent risk factor for mortality in sepsis and septic shock patients(29, 30). Furthermore, in children with severe infection, when either saline or albumin fluid boluses were administered over and above the maintenance fluids, the 48-hour mortality was significantly higher(31). These observations resulted in a feasibility RCT of conservative versus liberal approach to fluid therapy in septic shock (CLASSIC Trial). This trial highlighted feasibility for this approach with significantly lower cumulated resuscitation fluid in the ICU at day 5 after randomisation and during the entire ICU stay in the restriction group vs. the standard care group [mean differences −1.2 L (95 % CI −2.0 to −0.4); and −1.4 L (95 % CI −2.4 to −0.4); $P < 0.001$) without increasing the risk of adverse outcomes(32). A initial approach involving passive leg raising to assess fluid responsiveness may reduce the total volume of fluid administered in sepsis and septic shock patients(33).

Vasopressors and inotropic agents

Vasopressors, like fluids, are an intuitive component of resuscitation bundles. In theory, vasopressors correct excessive vasodilatation at the root of the alleged pathological causal pathway. However, hypotension does not necessarily signify impaired organ perfusion and normal blood pressure does not guarantee adequate tissue perfusion. By Poiseuille's law, the blood vessel's radius has a much more profound impact on flow than the pressure gradient. Because vasopressors induce vasoconstriction (i.e. reducing the radius of vessels), they may reduce organ perfusion despite achieving blood pressure targets. In addition, vasopressors themselves may impair microcirculatory

flow(34). For example, clinicians may be inclined to attribute worsening signs of shock to the underlying illness and intensify therapy, unsuspecting of the fact that it is their intervention that is the culprit. Accordingly, when administering vasoactive agents, clinicians should consider iatrogenic complications in the differential diagnosis of any clinical deterioration. Recent studies raise concern regarding the overall safety of liberal vasopressor use in sepsis. Until adequately powered clinical trials ascertain the overall effects of more restrictive MAP targets, the overall benefit of currently recommended MAP targets hinges on scant evidence(35).

When discussing vasopressor therapy, the role of relative vasopressin deficiency and utility of vasopressin as a vasopressor in septic shock have to be considered(36). In a trial of vasopressin versus norepinephrine and steroids versus placebo, using a factorial trial design, with renal failure free days as primary outcome, vasopressin compared with norepinephrine did not improve the number of kidney failure–free days(37). The hypothesis from sub-group analyses from earlier vasopressin trials(38), is that patients with lower severity of illness may benefit the most. This hypothesis should be tested in the context of increasing vasopressin use in patients with septic shock(39). The circulatory changes in sepsis could also be secondary to abnormalities in the renin-angiotensin system and exogenously administered exogenous angiotensin II could be an useful vasopressor in septic shock patients(40). Recently, in patients with catecholamine resistant vasodilatory shock, angiotensin II administration was associated with improved blood pressure, which was the primary outcome. In this trial, nearly 75% of patients the aetiology of catecholamine resistant vasodilatory state was septic shock, implying potential utility for angiotensin II in septic shock management, once mortality benefit is confirmed(41).

Levosimendan is a calcium-sensitising drug that has multiple effects aside from positive inotropy, which are potentially beneficial in sepsis. For example, in a recent pilot randomised controlled trial in 20 patients, levosimendan lowered the lactate/pyruvate ratio, which suggests beneficial effect on cellular metabolic alterations in septic shock(42). However, a large superiority trial that tested the hypothesis that levosimendan would reduce the severity of organ dysfunction in adults with sepsis, in 516 adult patients with sepsis, levosimendan compared to placebo was not associated with less severe organ dysfunction or lower mortality. Importantly there was a higher risk of supraventricular arrhythmias and weaning failure in the levosimendan treated patients in this trial(43). Given the lack of efficacy of levosimenden in cardiac surgical patients with impaired left ventricular function(44, 45),

further studies to enrich sepsis population that is likely to benefit from levosimenden is required prior to widespread clinical use.

Conclusions

Septic shock is common and carries a high risk of death. Early administration of antibiotics and targeted resuscitation remain the cornerstones of care. There is increasing evidence that some conventional approaches with large volume resuscitation and high-dose vasopressors may not be beneficial, or even potentially harmful. Distinction should be drawn between microcirculatory and macro-circulatory changes and resuscitation. Individualised resuscitation focused on microcirculation and lower blood pressure targets may have theoretical advantages over macro-circulatory goals of care applied invariably to all patients. However, conclusive evidence will require adequately powered experiments.

Key points

The Surviving sepsis campaign guidelines provide a framework for managing sepsis patients.

Early antibiotic therapy and fluid resuscitation are major interventions in sepsis patients.

Emerging evidence suggests discordance between macrocirculatory and microcirculatory optimisation following resuscitation.

As resuscitation-associated, positive fluid balance and high dose vasopressors are associated with adverse outcomes in septic shock, trials of fluid restriction and lower blood pressure targets are ongoing.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011 for MSH) and the Fonds de Recherche du Québec – Santé (33132 for FL).

Conflicts of interest

None.

References and recommended reading

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
2. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762-74.
3. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775-87.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51.
5. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.
6. Dünser MW, Takala J, Brunauer A, Bakker J. Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. Critical Care. 2013;17(5):326.
7. van Beest P, Lont M, Holman N, Loef B, Kuiper M, Boerma E. Central venous-arterial pCO2 difference as a tool in resuscitation of septic patients. Intensive Care Med. 2013;39:1034 - 9.
8. Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med. 2002;28(3):272-7.
9. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. Nature Reviews Disease Primers. 2016;2:16045.
10. Ince C, Mik EG. Microcirculatory and mitochondrial hypoxia in sepsis, shock, and resuscitation. Journal of applied physiology (Bethesda, Md : 1985). 2016;120(2):226-35.
11. Moore JP, Dyson A, Singer M, Fraser J. Microcirculatory dysfunction and resuscitation: why, when, and how. Br J Anaesth. 2015;115(3):366-75.
12. Matkovich SJ, Al Khiami B, Efimov IR, Evans S, Vader J, Jain A, et al. Widespread Down-Regulation of Cardiac Mitochondrial and Sarcomeric Genes in Patients With Sepsis. Crit Care Med. 2017;45(3):407-14.
13. Takasu O, Gaut JP, Watanabe E, To K, Fagley RE, Sato B, et al. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. Am J Respir Crit Care Med. 2013;187(5):509-17.
14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.

15. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41(9):1549-60.
16. Investigators P, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, et al. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med. 2017;376(23):2223-34.
17. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303(8):739-46.
18. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;182(6):752-61.
19. Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Heffner AC, Kline JA, et al. Prognostic value and agreement of achieving lactate clearance or central venous oxygen saturation goals during early sepsis resuscitation. Acad Emerg Med. 2012;19(3):252-8.
20. Vincent JL, Quintairos ESA, Couto L, Jr., Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016;20(1):257.
21. Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, Ameneiros-Rodriguez E, Donapetry-Garcia C, Vila-Altesor M, et al. Comprehensive review on lactate metabolism in human health. Mitochondrion. 2014;17:76-100.
22. Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. World journal of critical care medicine. 2016;5(1):47-56.
23. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017;151(6):1229-38.
24. Byrne L, Van Haren F. Fluid resuscitation in human sepsis: Time to rewrite history? Annals of Intensive Care. 2017;7:4.
25. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med. 2017;43(5):625-32.
26. Seethala RR, Hou PC, Aisiku IP, Frendl G, Park PK, Mikkelsen ME, et al. Early risk factors and the role of fluid administration in developing acute respiratory distress syndrome in septic patients. Ann Intensive Care. 2017;7(1):11.
27. Patel A, Pieper K, Myburgh JA, Perkovic V, Finfer S, Yang Q, et al. Reanalysis of the Crystalloid versus Hydroxyethyl Starch Trial (CHEST). N Engl J Med. 2017;377(3):298-300.
28. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412-21.

29. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, et al. Higher Fluid Balance Increases the Risk of Death From Sepsis: Results From a Large International Audit. Crit Care Med. 2017;45(3):386-94.
30. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017.
31. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after Fluid Bolus in African Children with Severe Infection. N Engl J Med. 2011;364(26):2483-95.
32. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-705.
33. Rameau A, de With E, Boerma EC. Passive leg raise testing effectively reduces fluid administration in septic shock after correction of non-compliance to test results. Ann Intensive Care. 2017;7(1):2.
34. Dubin A, Pozo MO, Casabella CA, Palizas F, Jr., Murias G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care. 2009;13(3):R92.
35. Lamontagne F, Marshall JC, Adhikari NKJ. Permissive hypotension during shock resuscitation: equipoise in all patients? Intensive Care Med. 2017.
36. Russell JA, Lee T, Singer J, Boyd JH, Walley KR, Vasopressin, et al. The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience. Crit Care Med. 2017;45(6):940-8.
37. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18.
38. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358(9):877-87.
39. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of Vasopressin Use for Adults with Septic Shock. Annals of the American Thoracic Society. 2016;13(10):1760-7.
40. Correa TD, Takala J, Jakob SM. Angiotensin II in septic shock. Crit Care. 2015;19:98.
41. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med. 2017;377(5):419-30.
42. Hajjej Z, Meddeb B, Sellami W, Labbene I, Morelli A, Ferjani M. Effects of Levosimendan on Cellular Metabolic Alterations in Patients With Septic Shock: A Randomized Controlled Pilot Study. Shock. 2017;48(3):307-12.
43. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. N Engl J Med. 2016;375(17):1638-48.
44. Landoni G, Lomivorotov VV, Alvaro G, Lobreglio R, Pisano A, Guarracino F, et al. Levosimendan for Hemodynamic Support after Cardiac Surgery. N Engl J Med. 2017;376(21):2021-31.

45. Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, et al. Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. N Engl J Med. 2017;376(21):2032-42.